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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,593	12/05/2001	Katherine S. Bowdish	1087-2	3532

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EXAMINER	
TUNGATURTHI, PARITHOSH K	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,593	BOWDISH ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18,19,22,23,36,44,45,85-90 and 96-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18,19,22,23,36,44,45,85-90 and 96-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/18/2006 has been entered.

2. Claims 1-16, 18, 19, 22, 23, 36, 44, 45, 85-90, and 96-99 are pending.

Claims 1, 5, 15, 16, 86, 87, 96 and 99 have been amended.

Claims 24-35, 37-43, 46-84 and 93-95 have been cancelled.

Claims 17, 20, 21, 91 and 92 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. Claims 11-16, 18, 19, 22, 23, 36, 44, 45, 85-90, and 96-99 are pending and under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. This office action contains New Grounds of Rejections.

Rejections Withdrawn

6. The rejection of claims 1-16, 18, 19, 22. 23, 36, 90 and 96-99 under 35 U.S.C. 103(a) as being unpatentable over Barbas et al (a) (WO 94/18221, published 8/94) and further in view of Dower et al (WO 96/40750, published 12/96) and Barbas et al (b) (PNAS 92:2529-2533, 1995) and in view of Kini et al (FEBS Letters. 1995, 375:15-17) are withdrawn in view of amendments to the claims: the claim are now amended to recite "wherein the immunoglobulin molecule or fragment thereof binds to and agonizes an EPO or TPO receptor".

Response to Arguments

7. The applicant argues (pages 10-12 of the response filed on 01/20/2006) that "there is no teachings or suggestion in Barbas (a) that CDR replaced antibodies could used to stimulate or agonize receptor function and/or receptor mediated events.....Kini fails to teach or suggest that an agonist peptide (such as EPO or TPO) should be incorporated into the CDR region of an immunoglobulin or a fragment thereof.....therefore, one of ordinary skill in the art would not be motivated to incorporate agonist peptides, such as the TPO peptides of Dower, into the CDR replaced antibodies of Barbas (a) or (b)..... no combination of the cited references teaches inserting agonist peptides into an immunoglobulin wherein the resulting immunoglobulin has an agonistic activity".

The applicants arguments in response to "no teachings or suggestion in the art that CDR replaced antibodies could used to stimulate or agonize receptor function and/or receptor mediated events" are found persuasive and hence the rejection of claims 1-16, 18, 19, 22. 23, 36, 90 and 96-99 as made in the previous action is withdrawn (please see above).

8. The rejection of claims 44, 45 and 85-89 under 35 U.S.C. 103(a) as obvious in light of Barbas et al (a) (WO 94/18221, published 8/94) and further in view of Dower et al (WO 96/40750, published 12/96) and Barbas et al (b) (PNAS 92:2529-2533, 1995) and in view of Kini et al (FEBS Letters, 1995. 375: 15-17) is maintained.

The applicant's argue that with respect the references cited by the Examiner, taken alone or in any combination, fail to teach or suggest an immunoglobulin molecule, or fragment thereof, wherein at least a portion of a CDR region is replaced with a biologically active peptide flanked with a proline at the carboxy terminus. In particular, the Examiner relies on Kini et al. for the use of prolines to bracket a peptide sequence... .....In contrast to the teachings of Kini et al., Applicants have found that addition of a proline residue at the carboxy terminus of a peptide which has been incorporated into a CDR region of an antibody provides superior results as compared to incorporation of a proline residue at the amino terminus of the peptide..... in particular table in Example 1 (pages 12-13 of the response filed on 01/20/2006)".

In response to the above arguments, the applicant is reminded the teachings of Kini et al wherein Kini et al teach a novel approach to the design of potent bioactive

peptides by incorporation of proline brackets (title in particular) and that proline residues help in the presentation of interaction sites and that it is logical to propose that the incorporation of proline residues around a bioactive peptide might enhance its potency significantly (see introduction on page 15) and as evidenced by the specification that the EPO and TPO mimetics are biologically active peptides, it would have been obvious and one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the biologically active peptides as modified, via incorporation of proline residues, by the teachings of Kini et al to in place of CDRs within a heavy or light chain as taught by Barbas (a). Kini et al teach that (please see results and discussion, in particular) proline brackets, introduce no undue strain along the backbone, and thus allow the flexibility of the interaction site. Kini et al show an increase in potency of 10- to 15-fold in the development of bioactive peptides. Thus, Kini et al teach that this novel approach of incorporation of peptide brackets provides a viable alternative to cyclization in the design and development of potent peptide drugs and ligands, a critical step in their development as drugs.

In response to the applicant arguments that "In contrast to the teachings of Kini et al., Applicants have found that addition of a proline residue at the carboxy terminus of a peptide which has been incorporated into a CDR region of an antibody provides superior results as compared to incorporation of a proline residue at the amino terminus of the peptide", the applicant is reminded that that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either

in the references themselves or in the knowledge generally available to one of ordinary skill in the art and as suggested by Kini et al for the addition of Proline brackets, it would be obvious to one of skill in the art to expect the "superior results" in contrast to the applicants arguments on page 12 of the response filed 01/20/2006. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the teachings of Barbas PCT in replacing CDRS in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and randomizing the flanking sequences for presenting a biological active peptide in a conformation for binding to a receptor for and the teachings of Dower et al indicating the peptide sequences of TPO that bind the thrombopoietin receptor and SEQ ID NO:2 without the proline at the C-terminus (which is SEQ ID NO:1, see page 26-30 and Table 7 and 9 and specifically page 76, top molecule which comprises SEQ ID NO:1 with cysteines flanking the sequence, and claim 19 which claims the sequence of SEQ ID NO:1 (see last compound) and the addition of flanking sequences for structural constraints (see page 45, lines 10-14) and the teachings of Barbas Publication teach replacement of CDR3 in the anti-tetanus toxoid antibody with several sequences and the teachings of Kini et al indicating the design of biologically active peptides with proline residues flanking the sequence and the prolines resulted in restricting the conformation and in enhanced activity of the peptides would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established

scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination. *In re Semaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

Further, not all the di-peptides in claim 86 consist of prolines. Thus, it is not clear as to the arguments on page 13 (paragraph 2, in particular), where the applicant points out the importance of addition of proline brackets to the CDR amino acid sequences because not all di-peptides as encompassed by claim 86 have prolines in them.

The applicants argue that they have unexpectedly found that Fab clones having a proline residue immediately flanking the carboxy terminus of an incorporated peptide (e.g., clones X1, X3a, X3b, X4b, X4c, X5a, X5c, and X7c) resulted in strong binders whereas Fab clones having a proline residue immediately flanking the amino terminus of an incorporated peptide did not result in strong binders (e.g., clone X1a) ..... Accordingly, the results obtained by Applicants for incorporation of a peptide into a CDR region are unexpected and nonobvious over the disclosure of Kini et al. relating to short peptides..... Accordingly, no combination of the cited references teaches or suggests the unexpected and superior results obtained atom inserting a proline residue at the carboxy terminus of a peptide that has been incorporated into the CDR region of an immunoglobulin molecule. Therefore, claims 44-45, 85, and 87-89, are novel and non-obvious in view of the cited references (page 13 of the response filed on 01/20/2006, paragraphs 1 and 2 in particular).

In response to the applicants arguments that the "applicants have unexpectedly found that Fab clones having a proline...." (page 13 of the response filed on 01/20/2006), the applicant is directed to MPEPE 716.01 (C) I and II wherein it states that

> Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that unexpected results must be established by factual evidence." "[A]ppellants have not presented any experimental data showing that prior heat-shrinkable articles split. Due to the absence of tests comparing appellant's heat shrinkable articles with those of the closest prior art, we conclude that appellant's assertions of unexpected results constitute mere argument."). See also In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); Ex parte George, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991).
>
> The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See MPEP § 2145 generally for case law pertinent to the consideration of applicant's rebuttal arguments.

The data presented by the applicant is not found persuasive to be unexpected and unobvious and hence, the argument is considered to be moot.

In addition, the argument of unexpected results is not commensurate in scope with claims 1-16, 18, 19, 22, 23, 36, 86, 90 and 96-99, because these claims do not require proline at the C-terminus.

With respect to claim 86, the applicants argue (please see pages 13-15 of the response filed on 01/20/2006) that Barbas et al. (a) fails to teach or suggest that a dipeptide amino acid sequence should be introduced flanking the peptide, fails to teach or suggest the specific dipeptide amino acid sequences provided in claim 86, and fails to teach or suggest that such amino acid sequences should be incorporated at the carboxy terminus of the peptide introduced into the CDR region. In particular, Barbas et al. (a) teaches that the flanking regions of the peptide incorporated into the CDR region may be randomized based on the following equation: -X-$(MNN)_a$-Y-$(MNN)_b$-X-, wherein ..... this equation provides an almost endless number of possible combinations of flanking residues for the incorporated polypeptide ..... there is no teaching or suggestion of the particular dipeptide amino acid sequences listed in claim 86 of the instant application..... accordingly claim 86 is novel and non-obvious in view of the cited references.

In response to this argument, the applicant is again reminded that the claim broadly recites "at least a portion of CDR are replaced with a biologically active peptide and the biologically active peptide is flanked at its carboxy terminus with an amino acid sequence selected from the group consisting of a list as claimed". Hence any biologically active peptide of any length including as explained by Barbas (a) et al (see page 14 of the response filed on 01/20/2006 and as stated above for the explanation of the Barbas (a)). In addition, a more clearer citation is on page 86 of Barbas(a) wherein the RGD sequence was the peptide sequence and three amino acids on each side were added (see page 86, lines 1-7).

New Grounds of Rejection

9. Claims 44, 45, 85--89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 44, 45, 85--89 are indefinite for reciting "biologically active peptide" for the exact meaning of the phrase is not clear. What biologically activity is the applicant referring to? Is it the antigen binding affinity, protein activation or protein inactivation? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 1-16, 18, 19, 22. 23. 36, 44, 45, 85-90, 96-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas et al (a) (WO 94/18221, published 8/94; cited in the previous office action mailed 10/18/2005) and further in view of Dower et al (WO 96/40750, published 12/96; cited in the previous office action mailed 10/18/2005) and Barbas et al (b) (PNAS 92:2529-2533, 1995; cited in the previous office action mailed 10/18/2005) and in view of Kini et al (FEBS Letters. 1995, 375:15-17; cited in the previous office action mailed 10/18/2005) and in view of Cwirla et al (Science, Vol, 276 13 June 1997; IDS 8.15.2005) and further in view of Wrighton et al. (Science. 1996. 273, 458-463) as evidenced by Helms (Protein Science. 1995, 4:2073-2081; cited in the previous office action mailed 08/20/2003).

The claims are summarized as an immunoglobulin or fragment thereof comprising a region wherein the amino acid residues corresponding to at least a portion of a CDR replaces with a peptide mimetic selected from the group of EPO and TPO, wherein the immunoglobulin molecule fragment thereof binds to and agonizes an EPO or TPO receptor, wherein the immunoglobulin or fragment is anti-tetanus toxoid and a human antibody and comprising wherein the residues corresponding to at least a portion of at least one or two CDRS are replaced with SEQ ID NO:2 or SEQ ID NO:1 with a proline added at the N and/or C terminus wherein the fragment is a Fab or full IgG from and the CDR is on a light chain and/or a heavy chain and the CDR is CDR3 and/or CDR1 or CDR2, and the peptide is flanked by a proline at the C terminus and has an amino acid at its N terminus and the flanking sequence is from several two amino acid peptides (claims 86-89) and compositions comprising such.

Barbas et al teach replacing CDRS in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and randomizing the flanking sequences for presenting a biological active peptide in a conformation for binding to a receptor for example (see page 5, 8, 17, lines 5-33, page 19-20, page 26-27, 28-29, 53, 144, 149). Barbas et al also teach that adding the peptide RGD by itself to the CDR resulted in no activity because of flanking residues needed to be added to optimize the conformation (see page 84, lines 8-31).

Barbas et al (a) does not teach replacing a CDR with an TPO mimetic of SEQ ID NO:2 or SEQ ID NO:1 with proline flanking the sequence (which is SEQ ID NO:2) which can function as an agonist or the scaffold is the anti-tetanus toxoid antibody. These deficiencies are made up for in the teachings of Dower et al and Barbas et al (b), Kini et al, Cwirla et al and Wrighton et al.

Dower et al teach peptide sequences of TPO that bind the thrombopoietin receptor and SEQ ID NO:2 without the proline at the C-terminus (which is SEQ ID NO:1, see page 26-30 and Table 7 and 9 and specifically page 76, top molecule which comprises SEQ ID NO:1 with cysteines flanking the sequence, and claim 19 which claims the sequence of SEQ ID NO:1 (see last compound) and the addition of flanking sequences for structural constraints (see page 45, lines 10-14).

Barbas et al (b) teach replacement of CDR3 in the anti-tetanus toxoid antibody with several sequences.

Kini et al teach the design of biologically active peptides with proline residues flanking the sequence and the prolines resulted in restricting the conformation and in enhanced activity of the peptides (see entire document). Kini et al also teach that (please see results and discussion, in particular) proline brackets, introduce no undue strain along the backbone, and thus allow the flexibility of the interaction site. Kini et al show an increase in potency of 10- to 15-fold in the development of bioactive peptides. In addition to showing that the peptide with complete proline brackets inhibits platelet aggregation, and that by simply including proline brackets, they have obtained a potent ant platelet peptide that should provide a strong starting point for the development of

more potent antithrombotic peptides. Thus, Kini et al teach that this novel approach of incorporation of peptide brackets provides a viable alternative to cyclization in the design and development of potent peptide drugs and ligands, a critical step in their development as drugs.

Cwirla teaches that the 14 amino acid TPO peptide that is 100 % identical to the TPO peptide as claimed can act as a potent agonist of the TPO and as a potent natural cytokine.

Wrighton et al teach small peptides as potent mimetics of the protein hormone EPO (abstract in particular). Wrighton et al, through random phage display isolate small peptides that bind to and activate the receptor for the cytokine EPO, and show that the peptides act as agonists and stimulate erythropeoiesis in mice. Wrighton et al show that the signaling pathways activate by these peptides appear to be identical to those induced by the natural ligand.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an immunoglobulin or fragment thereof comprising a region where amino acid residues corresponding to at least a portion of a CDR replaces with a peptide mimetic selected from the group of EPO and TPO, wherein the immunoglobulin molecule fragment thereof binds to and agonizes an EPO or TPO receptor, wherein the immunoglobulin or fragment is anti-tetanus toxoid and a human antibody and comprising wherein the residues corresponding to at least a portion of at least one or two CDRS are replaced with SEQ ID NO:1 or SEQ ID NO:2.

It is noted that the applicant argued (in the response filed on 01/20/2006) that there would be no motivation for one skill in the art to combine the teachings of Barbas (a) with the teachings of Dower because Barbas (a) teaches method for designing and using CDR replaced antibodies that antagonize receptor function while Dower discloses TPO agonist peptides; and because Kini merely proposes that proline residues flanking protein-protein interaction sites perform a structural role in enhancing their interaction and fails to teach or suggest that an agonist peptide (such as EPO or TPO) should be incorporated into the CDR region of an immunoglobulin or a fragment thereof.

In addition to the response to the arguments discussed above, the applicant is reminded that Barbas et al (a) teach antibodies with several peptide sequences replacing the CDRS in an antibody and the molecules bind the target receptor and suggest that other sequences for other receptors would also work in replacing the CDRS (see pages 24- 27) and the need to constrain the peptide: (see page 28-29) and because Barbas et al (b) teach replacement in the anti-tetanus antibody of unrelated sequences from that in the CDR and the antibody binds the target and since antibody tertiary structures are homologous one skill in the art would conclude that the anti-tetanus antibody could be used for other sequences to present.

Hence, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have combined the above teachings of Barbas et al (a) and Barbas et al (b) with Dower et al and Kini et al because Dower et al

specifically teach peptides that are fusion proteins and that the peptides need to be constrained to be active and because Kini et al teach that proline residues prevent the extension of neighboring secondary structures and thus protect the conformation and integrity of interaction sites (see page 15) and since prolines limit the flexibility around the alpha-carbon atoms, the number of possible conformations would be drastically reduced (see page 16) and the peptides with the prolines resulted in better activity (please see the discussion of Kini et al wherein the detailed explanation of the advantages of proline brackets to biologically active peptides is discussed).

Moreover, one of ordinary skill in the art would have known to use an antibody as a scaffold to present the TPO peptide because in solution peptides can be a random configuration and the scaffold constrains the peptide and presents it in a conformation that is better for binding and it would have been obvious to have residues flanking the sequence for presentation and it would have been obvious to use a proline at the C-terminus because of the teachings by Barbas et al (a) as discussed above and as taught by Kini et al it is known in the art that proline residues decrease the conformational flexibility of a peptide and thus would constrain the peptide and as evidenced by Helms et al it is known in the art that proline residues decrease the conformational flexibility of a peptide (see page 2078) and thus would constrain the peptide.

Furthermore, it would have been obvious to place the peptide in a CDR because Barbas et al (a) teach human antibodies have benefits of therapy in vivo in humans for blocking or inhibiting the target and in view of Dower et al who teach that the TPO

peptides can be used for therapy, one would have motivation to add the peptide to the antibody CDR and use as agonists as taught by Cwirla et al and Wrighton et al., because Cwirla teaches that the 14 amino acid TPO peptide that is 100 % identical to the TPO peptide as claimed can act as a potent agonist of the TPO and as a potent natural cytokine, and Wrighton et al, through random phage display isolate small peptides that bind to and activate the receptor for the cytokine EPO, and show that the peptides act as agonists and stimulate erythropeoiesis in mice.

Thus it would have been obvious to one skilled in the art to have produced the an immunoglobulin or fragment thereof comprising a region where amino acid residues corresponding to at least a proline of a CDR replaces with a peptide mimetic selected from the group of EPO and TPO, wherein the immunoglobulin molecule fragment thereof binds to and agonizes an EPO or TPO receptor, wherein the immunoglobulin or fragment is anti-tetanus toxoid and a human antibody

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Johnson et al. 1998. Biochemistry, 37:3699-3710.

Conclusion

12. No claims are allowed

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

14. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER